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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,636	04/17/2001	Srikanth Venkatraman	IN01155K	7298

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/23/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,636	VENKATRAMAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-39* is/are pending in the application.

4a) Of the above claim(s) *24,25 and 32-39* is/are withdrawn from consideration.

5)☒ Claim(s) *27* is/are allowed.

6)☒ Claim(s) *1-22, 26 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 14 (filed 6/24/03) claims 1, 21, 22, 26-31 have been amended, claim 23 cancelled, and claims 32-39 added. Claims 1-22, 24-39 are pending. Claims 24-25 remain withdrawn from consideration; claims 32-39 are also withdrawn from consideration. Claims 1-22, 26-31 are examined in this Office action.

Applicants' arguments filed 6/24/03 have been considered and found not persuasive.

*

The specification is objected to. On page 1, line 7, and page 6, line 7, an unidentified serial number is referred to.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The cited claims assert that the compounds (of claim 27) are "therapeutically effective". However, no evidence has been presented that the claimed compounds (or

compositions) are "therapeutically effective" to treat at least one human disease.

Applicants have demonstrated only inhibition of HCV NS3/NS4a serine protease. It is stipulated that such inhibition will occur *in vivo*. But that does not, in and of itself, translate into an effective therapy of a hepatitis infection. A key issue is whether the NS3/NS4a protease can be inhibited to a sufficient degree to cause an actual reduction in population of the virions. Issues such as proper anatomical localization, bioavailability, susceptibility of the claimed compounds to proteases and monooxygenases would have to be addressed. For example, if the virus is replicating at a rate of 100 "units" per day in the absence of the compound, and 90 units per day in the presence of the compound, one could say that inhibition had been achieved. However, if the virus is replicating at a rate of 90 per day in spite of the presence of the compound (of claim 1), the patient's condition will still worsen, and "treatment" will not have been achieved. As it happens, structure/activity relationships are unpredictable. As observed by Tung (WO 98/17679), compounds within that disclosed genus (table 9, pp. 106-107) exhibited more than a 100-fold range of efficacies in the inhibition of HCV NS3 protease. Many of those compounds characterized as exhibiting an inhibition above 100 *micro*molar may have been completely inactive. (See also table I of WO 99/07734). Thus, one question is, can applicants look at a structure and determine its activity, even *in vitro*? And if not, how can applicants make predictions about what will happen *in vivo*? As

stated in Ingallinella (*Biochemistry* **37**, 8906, 1998) at page 8906, col 1:

"Neither an effective therapy for hepatitis C-associated chronic hepatitis nor a vaccine for preventing HCV infection has... been developed.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As it happens, effective treatment of viral infections such as hepatitis cannot be predicted from *in vitro* data alone; undue experimentation would be required to practice the claimed invention. It is suggested that the term "therapeutically effective" be deleted.

*

Claims 1-22, 26 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The definition of "E, X, and Y" spans 19 lines of text. In the 17th line of text, the following is recited: sulfonamide, , alkyl amines. Here, there are two consecutive

commas. One such comma is sufficient.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 are rejected under 35 U.S.C. §102(a) as being anticipated by Marchetti (*Synlett (Spec.)*, 1000-1002, 1999).

Marchetti discloses compound 3. As indicated previously, this compound anticipates a compound within the claimed genus when the substituent variables correspond as follows:

R3 = $HOOC\text{-}CH_2\text{-}CH_2\text{-}$
Z = N
R4 = H
W = >C=O
Y = $\text{-}CH_2\text{-}$ which is "substituted" with alkylamido

X = aryl ether (specifically, biphenyl ether)
A = $-CH_2-$
E = absent
G = $-(CH_2)_p$, wherein "p" is zero
Q = -NH-
V = >CH-
R2 = $-CH_2-SH$
R1 = -COOH

In response to this, applicants have amended claim 1 to recite that R1 is not a carboxylic acid when the substituent variables correspond as follows:

R3 = $HOOC-CH_2-CH_2-$
Z = N
R4 = H
W = >C=O
Y = $-CH_2-$ which is "substituted" with alkylamido
X = aryl ether (specifically, biphenyl ether)
A = $-CH_2-$
E = absent
G = $-(CH_2)_p$, wherein "p" is zero
Q = -NH-
V = >CH-
R2 = -COOH

However, this is not effective to exclude compound 3 of Marchetti for each of several reasons. First, claim 1 does not exclude the case of variable R2 representing $-CH_2-SH$. Second, claim 1 does not exclude the case of variable "Y" representing a methylene group that is "substituted" with alkylamido. Third, there are multiple ways of describing compound 3 (of Marchetti) using applicants' substituent variables. For

example, instead of stating that variable "A" is methylene while "E" is absent, it can be just as easily argued that the disclosed structure is arrived at when "A" is $(CHR)_p$, "E" is a one-carbon "alkyl" and integer variable "p" is zero. Alternatively, instead of stating that variable "A" is methylene while "G" is absent, one can argue that "A" is a bond, "G" is $-(CH_2)_p-$, and "p" is one.

Thus, for each of several reasons, the recited proviso does not exclude compound 3 of Marchetti. The claims remain anticipated.

*

Claims 1-2 are rejected under 35 U.S.C. §102(a) as being anticipated by Marchetti (*Synlett (Spec.)*, 1000-1002, 1999).

Marchetti discloses compound 10. This compound anticipates a compound within the claimed genus when the substituent variables correspond as follows:

R3 = tButyl-OOC-CH_2-CH_2-
Z = N
R4 = H
W = >C=O
Y = -CH_2- which is "substituted" with alkylamido
X = aryl ether (specifically, biphenyl ether)
A = -CH_2-
E = absent
G = -$(CH_2)_p$, wherein "p" is zero
Q = -NH-
V = >CH-
R2 = -CH_2-SH
R1 = -COOH

Thus, the claims are anticipated.

*

Claims 1-2 are rejected under 35 U.S.C. §102(a) as being anticipated by Marchetti (*Synlett (Spec.)*, 1000-1002, 1999).

Marchetti discloses compound 17. This compound anticipates a compound within the claimed genus when the substituent variables correspond as follows:

R3 = tButyl-OOC-CH_2-CH_2-
Z = N
R4 = H
W = >C=O
Y = methylamino which is "substituted" first with methoxycarbonyl, then with "alkylaryl"
X = aryl ether (specifically, biphenyl ether)
A = -CH_2-
E = absent
G = -$(CH_2)_p$, wherein "p" is zero
Q = -NH-
V = >CH-
R2 = -CH_2-SH
R1 = -COOH

Thus, the claims are anticipated.

*

Claims 1-2, 21 are rejected under 35 U.S.C. §102(b) as being anticipated by Fossli (USP 4,956,344).

As indicated previously, Fossli discloses the tripeptide pGlu-His-Gly. In response,

applicants have added a proviso to the claim. However, claim 1 still permits the "macrocycle" (containining Z,W, Y, X, A, E, G, V and Q) to represent pyroglutamic acid, claim 1 still permits R^2 to represent the side chain of histidine, and R^1 to represent glycine. If applicants believe that the provisos exclude the tripeptide in question, it is suggested that applicants explain how it is possible to reach this conclusion.

The rejection is maintained.

*

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by Reichelt (USP 4,260,601).

Reichelt discloses (col 8, line 65) the dipeptide Z-pGlu-His-OH. This compound is encompassed by the claimed genus when the substituent variables correspond as follows:

R3 = H
Z = CH
R4 = H
W = absent
Y = absent
X = absent
A = $-(CH_2)_p$, wherein "p" is zero
E = absent
G = $-(CH_2)_p$, wherein "p" is zero
Q = NR
R = carbamate
V = CH
R2 = H
R1 = COOH

R2 = side chain of histidine

Thus, the claims are anticipated.

*

Claims 1-2, 21 are rejected under 35 U.S.C. §102(e) as being anticipated by Dressen (USP 6,407,066).

Dressen discloses (col 16, line 11) the following dipeptide (wherein "Bz" represents benzyl):

Bz-pGlu-Phe-OH

This compound is encompassed by the claimed genus when the substituent variables correspond as follows:

R3 = H
Z = CH
R4 = H
W = absent
Y = absent
X = absent
A = $-(CH_2)_p$, wherein "p" is zero
E = absent
G = $-(CH_2)_p$, wherein "p" is zero
Q = NR
R = benzyl
V = CH
R2 = benzyl
R1 = COOH

Thus, the claims are anticipated.

*

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by Koiso (*Journal of Antibiotics* **47**, 765, 1994).

Koiso discloses (page 766) compound 1d. This is encompassed by claim 1 when the substituent variables correspond as follows:

E = an alkyl phenyl ether
Y = alkyl substituted with methylamino and with hydroxyl
X = absent
A = a covalent bond.
R2 = hydrogen
R1 = COOH

Thus, the claims are anticipated.

*

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by Laerum (USP 4,499,081).

Laerum discloses (col 2, line 11+) the following peptide:

pGlu-Glu-Asp-Cys-Lys

This compound is encompassed by the claimed genus when the substituent variables correspond as follows:

R3 = H
Z = CH
R4 = H
W = absent

Y = absent
X = absent
A = -$(CH_2)_p$, wherein "p" is zero
E = absent
G = -$(CH_2)_p$, wherein "p" is zero
Q = NH
V = CH
R2 = H
R1 = COR5
R5 = $N(R^9)R^{10}$
R9 = H
R10 = $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOH$
R11 = H
R1' = alkyl substituted with COOH
R2' = alkyl substituted with thio
R3' = alkyl substituted with amino

Thus, the claims are anticipated.

*

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by Shibuya C. (JP 53-77083)

Shibuya discloses various compounds which anticipate the claimed invention. For example, there is a structure provided at the top of page 677 in the left-hand column. This compound falls within the scope of claim 1 when "G" is carbonyl, "Q" is absent, "Z" is CH, "R3" is hydrogen, "R2" is phenyl and R12 is substituted heteroalkyl.

Thus, the claims are anticipated.

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-2 are rejected under 35 U.S.C. §103 as being unpatentable over Marchetti (*Synlett (Spec.)*, 1000-1002, 1999).

Marchetti discloses compound 3. As indicated previously, this compound anticipates a compound within the claimed genus when the substituent variables correspond as follows:

R3 = $HOOC\text{-}CH_2\text{-}CH_2\text{-}$
Z = N
R4 = H
W = >C=O

Y = $-CH_2-$ which is "substituted" with alkylamido
X = aryl ether (specifically, biphenyl ether)
A = $-CH_2-$
E = absent
G = $-(CH_2)_p$, wherein "p" is zero
Q = -NH-
V = >CH-
R2 = $-CH_2-SH$
R1 = -COOH

However, this is not, *per se*, the basis of this rejection. This ground of rejection is predicated on the assumption that applicants will, at some point in the future, successfully exclude compound 3 from the claimed genus. Should that event come to pass, this ground of rejection will then apply. The argument will then be that, even if the compound in which variable R3 represents the side chain of glutamic acid (i.e., carboxyethylene) has been excluded, the claim will still be rendered obvious. The reason is that the claims also encompass the possibility of R3 representing the side chain of aspartic acid (i.e., carboxylmethylene) as well as the possibility of R3 representing carboxybutylene. The moieties carboxylmethylene and carboxybutylene are homologs of the group carboxylethylene, differing only by one methylene group. As such, the skilled medicinal chemist would have expected substantially identical activity for compounds bearing one of the two homologous groups in question, i.e., carboxylethylene *versus* carboxylmethylene, or carboxyethylene *versus* carboxybutylene. [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)].

Thus, even if compound 3 (of Marchetti) is ultimately excluded from the claimed genus, the claims will still be rendered obvious.

*

Claims 21, 22 26 are rejected under 35 U.S.C. §103 as being unpatentable over Marchetti (*Synlett (Spec.)*, 1000-1002, 1999) or Koiso (*Journal of Antibiotics* **47**, 765, 1994).

The compounds disclosed by the references are indicated above. Neither reference discloses the combination of the compounds with a pharmaceutically acceptable carrier. However, methods of making such compositions are known to the drug formulation specialist of ordinary skill.

Thus, the claims are rendered obvious.

*

DAVID LUKTON
PATENT EXAMINER
GROUP 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.